Original Research Article

A Study of Correlation of NLR Ratio with Severity of Covid 19 Positive Patients

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Abstract

Coronavirus is a huge virus family which includes Middle East respiratory syndrome and severe acute respiratory syndrome. All of these are recognized to be the root of the common cold and more severe infections. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of SARSCoV-2 constituted a Public Health Emergency of International Concern (PHEIC). Compared to seasonal flu, covid 19 is more contagious, has a much longer incubation period, and is association with higher hospitalization, and mortality rates. There is a rapid unpredictable deterioration of the patient, therefore it requires timely prediction of the course and severity of the illness. Due to their simplicity of measurement, availability, affordability, and reliability, the differential blood cell counts can be employed as a measure of the intensity of the immune response. Neutrophil-lymphocyte ratio (NLR) plays a predictive function in a number of inflammatory illnesses and oncological processes. For Covid-19 patients, NLR has been demonstrated to be an independent risk factor for severe disease. The elevated NLR may be due to dysregulated expression of inflammatory cytokines. In this study we aim to study the correlation of NLR ratio with Covid 19 Positive patients.

Keywords: COVID-19, NLR, Neutrophils, D-dimer, CRP.

Introduction

Coronavirus is a huge virus family which includes Middle East respiratory syndrome and severe acute respiratory syndrome. All of these are recognized to be the root of the common cold and more severe infections. On 30 January 2020, the World Health Organization (WHO) declared that the outbreak of SARSCoV-2 constituted a Public Health Emergency of International Concern (PHEIC). [1-3]

Compared to seasonal flu, covid 19 is more contagious, has a much longer incubation period, and is association with higher hospitalization, and mortality rates. There is a rapid unpredictable deterioration of the patient, therefore it requires timely prediction of the course and severity of the illness. [1] Critically ill patients developed acute respiratory failure, acute respiratory distress syndrome, metabolic acidosis, coagulopathy, and septic shock as the condition advances. Early prognostic prediction can lessen fatality rates and ease the shortage of medical resources. [4-9]

In the systemic inflammatory response to severe infection, injury, polytrauma, and shock, white blood cells such as monocytes, lymphocytes and neutrophils are crucial players. Due to their simplicity of measurement, availability, affordability, and reliability, the differential blood cell counts can be employed as a measure of the intensity of the immune response. [11] Neutrophil-lymphocyte ratio (NLR) plays a predictive function in a number of inflammatory illnesses and oncological processes. The neutrophil to lymphocyte ratio (NLR), which is a ratio between the absolute neutrophil and absolute lymphocyte counts of a complete blood count, is the commonly used indicator of the systemic inflammatory response. [1-2]

For Covid-19 patients, NLR has been demonstrated to be an independent risk factor for severe disease. The elevated NLR may be due to dysregulated expression of inflammatory cytokines, aberrant rise of pathological low-density neutrophil and the upregulation of genes are involved in lymphocyte cell death pathway, which are caused by the mechanism of SARS-CoV-2 infection. [7-8] In

severe or non-survival patients suffering with Covid-19, the count of lymphocytes decreases progressively, whereas there is gradual increase in the count of neutrophils. [1-8]

Aims and objectives

*   To assess correlation of NLR ratio with severity of Covid 19 positive patients at the time of presentation.
*   To identify the association of NLR ratio with treatment outcomes in Covid 19 positive patients.
*   To assess relation of NLR ratio with other inflammatory markers used in Covid 19 patients (D- dimer, serum ferritin, CRP).

Materials and methodology

Study Place: Tertiary care hospital, South Gujarat, India

Study Design: Retrospective/ cross sectional study

Study Subject: Two hundred cases of covid 19 positive patients admitted in Covid positive wards in Tertiary care hospital, South Gujarat, from the months of June 2020 to December 2020 were taken as sample population after calculating and comparing with total population and applying Solvin's formula.

Inclusion Criteria:-

Adult patients of both sexes admitted in covid 19 positive wards diagnosed as covid 19 positive –

*   Rtpcr positive
*   Rapid antigen test positive
*   Cases in which there is availability of CBC (complete blood counts) and inflammatory

marker reports (Serum Ferritin, D-dimer, CRP) with case sheets.

Exclusion criteria :-

*   Pregnant females
*   Paediatric age group
*   HIV positive patients
*   Immuno-compromised patients
*   Patients on chemotherapy
*   Patients with other immune deficiency diseases.
*   Acute and chronic leukemias, lymphomas and other blood dyscrasias.

Duration of study: From time of ethical clearance to 30th OCT 2022

Methodology:

Data of covid 19 positive patients (who come under the inclusion criteria) selected by purposive sampling method were collected and analysed on the basis of their clinical symptoms and severity of disease at the time of presentation. The data regarding outcomes of the patient was also be gathered. The data regarding their basic blood tests including complete blood counts, their inflammatory markers (D dimer, serum ferritin, CRP) was also collected. This collected data was used to find correlation between severity of patients on presentation with NLR ratio (obtained from CBC report).

Study Variables:

The clinical outcome of the patient was correlated with NLR ratio. Association between the NLR ratio with other inflammatory markers was assessed.

Results

Table 1: Distribution as per clinical severity of Covid-19 patients

Severity	Frequency	Percent
Mild	82	41.0%
Moderate	82	41.0%
Severe	36	18.0%
Total	200	100.0%

Graph- Distribution as per clinical severity of Covid-19 patients
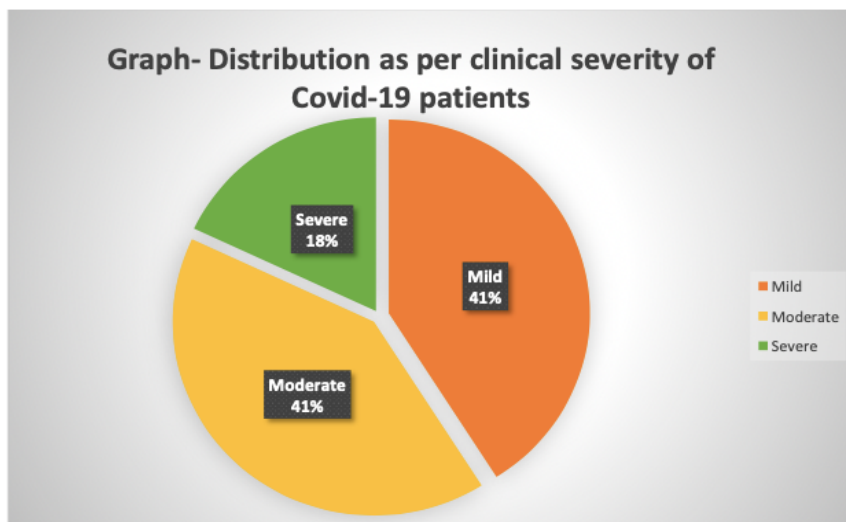
Table 5: Correlation of lab results with severity of COVID-19 patients.

Laboratory results	Mild		Moderate		Severe		P value
	Mean	SD	Mean	SD	Mean	SD	
Lymphocytes	884.16	91.236	842.07	120.374	656.92	148.586	<0.001
Neutrophils	2646.32	188.556	3083.94	582.573	3503.86	601.890	<0.001
D-dimer(ng/mL)	426.61	282.761	744.99	309.939	1543.97	878.508	<0.001
CRP (mg/dL)	33.26	10.039	40.44	17.167	63.67	22.054	<0.001
Ferritin (ng/ml)	993.01	368.140	1142.66	216.039	1186.00	182.797	<0.001

Graph: Correlation of lab results with severity of COVID-19 patients
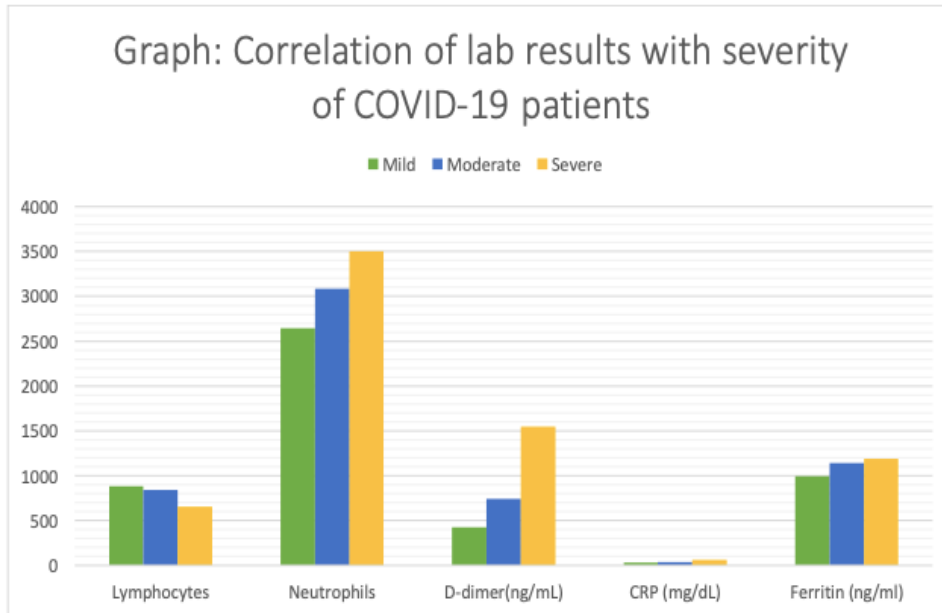
Table 6: Comparing co-morbidity with clinical severity of Covid-19 patients

			Clinical Severity			Total	P value
			Mild	Moderate	Severe		
Co-morbidities	ASTHMA	Count	4	1	1	6	0.071
		%	66.7%	16.6%	16.6%	100%	
	COPD	Count	0	1	2	3	0.688
		%	0.0%	33.3%	66.7%	100%	
	IHD	Count	0	8	5	13	<0.001
		%	0.0%	61.6%	38.4%	100%	
	DM	Count	4	9	7	20	0.008
		%	20%	45%	35%	100%	
	EPILEPSY	Count	2	0	0	2	0.06
		%	100%	0.0%	0.0%	100%	
	HTN	Count	10	18	8	36	0.034
		%	27.8%	50%	22.2%	100%	

Clinical Severity	Mean	SD	P value
Mild	3.0391	.53168	<0.001
Moderate	3.7607	1.01051	
Severe	5.5426	1.32315	

Graph: Comparing mean NLR values with Clinical severity of Covid-19

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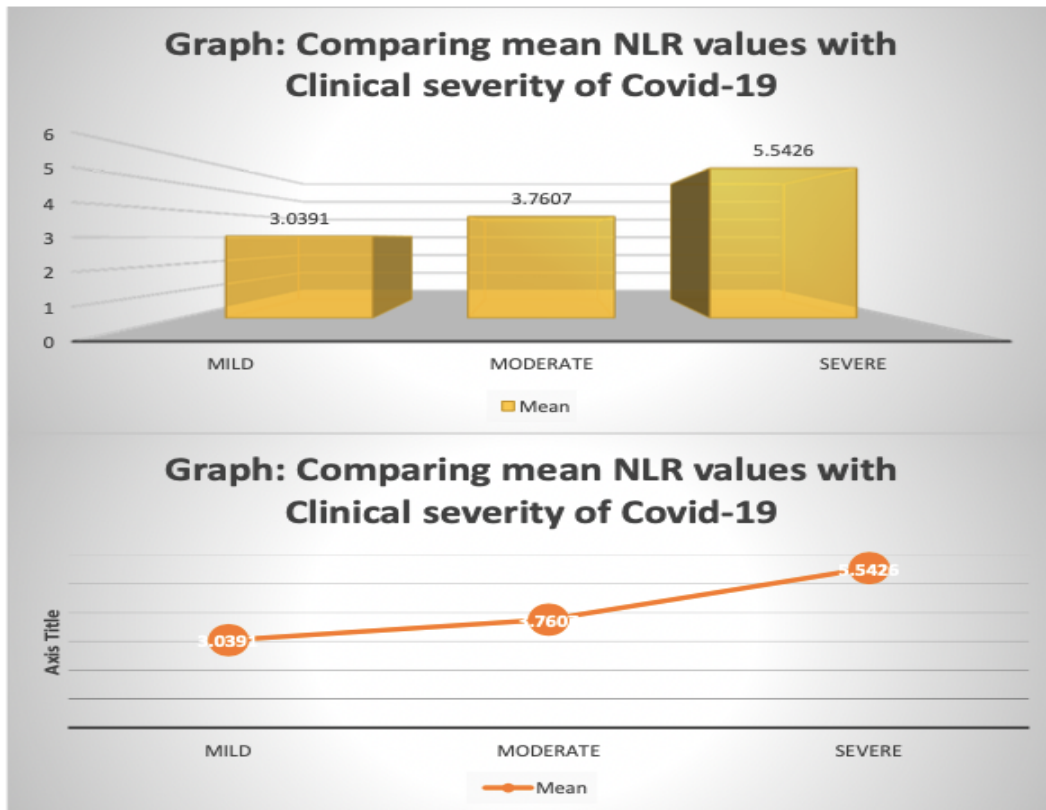
TABLE 9: Correlation of lab results of COVID -19 patients with outcome

Lab characteristics	Improved		Expired		P value
	Mean	SD	Mean	SD	
Lymphocytes	877.10	86.891	719.88	170.121	<0.001
Neutrophils	2759.33	363.726	3438.62	624.661	<0.001
CRP (mg/dL)	35.39	13.303	54.72	22.465	<0.001
D-dimer(ng/mL)	558.54	361.295	1173.09	775.259	<0.001
Ferritin (ng/ml)	1036.68	319.562	1197.98	194.954	<0.001

Table 12: ROC analysis for Area under the curve of different variables

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	P value.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Lymphocytes	.221	.037	<0.001	.149	.292
Neutrophils	.845	.031	<0.001	.784	.906
NLR	.912	.020	<0.001	.872	.952
D-dimer(ng/mL)	.807	.034	<0.001	.740	.874
CRP (mg/dL)	.751	.037	<0.001	.678	.824
Ferritin (ng/ml)	.655	.040	<0.001	.576	.734
The test result variable(s): Lymphocytes, Neutrophils , NLR, D-dimer, CRP, Ferritin has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

Diagonal segments are produced by ties.
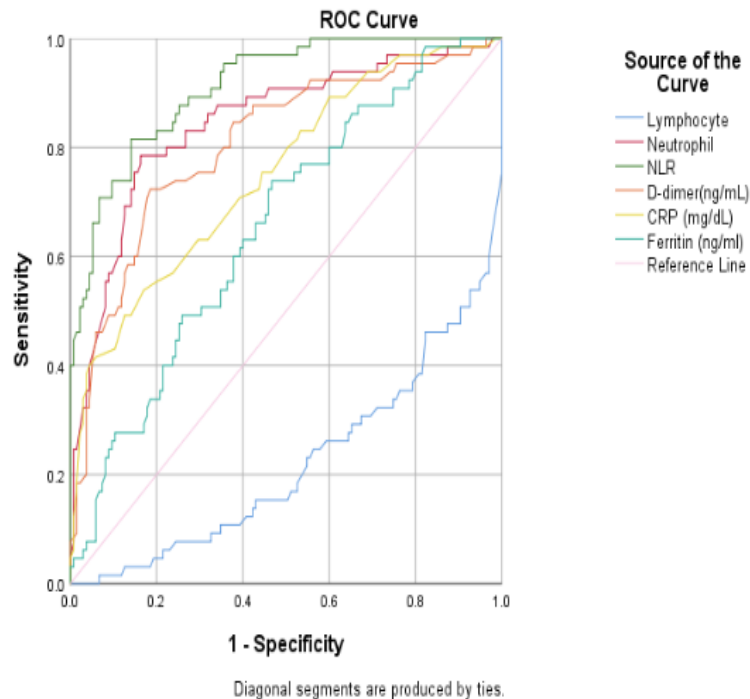
Discussion

This was a retrospective cross-sectional study to analyze the assessment of "NLR" (neutrophil to lymphocyte ratio) in Covid 19 positive patients. The data regarding their basic blood tests including complete blood counts, their inflammatory markers (D dimer, serum ferritin, CRP) were collected. This collected data was used to find correlation between clinical severity of patients on presentation with NLR ratio (obtained from CBC report). The clinical outcome of the patient will also be correlated with NLR ratio. A total of 200 patients were recruited in the present study. Distribution as per clinical severity of Covid-19 patients showed that out of 200 patients there were 82 (41%) mild cases, 82 (41%) moderate cases and there were 36 (18%) severe cases in present study.

1. On comparing mean age with clinical severity, a significant difference was obtained as revealed by the significant p value of <0.001. Severe covid-19 cases were much older than moderate than mild. This highlights that old age is one of the significant risk factors for developing severe covid-19 infection. [20-23]

2. On comparing sex distribution with clinical severity, no significant difference was observed in term of sex distribution between clinical severities. The p value for comparison was 0.272. [22-23]

3. On comparing clinical characteristics at presentation with severity of covid-19 patients a significant difference in terms of pulse rate (p<0.0010, respiratory rates (p<0.001) and oxygen saturation (p<0.001) was observed. No significant correlation was found between patients' temperature and blood pressure with clinical severity. This confirmed that severe patients have significantly more abnormal vitals at presentation in this study. [21,24]

4. On comparing the lab results with severity of COVID-19 patients a significant difference was observed as revealed by the p value of <0.001. Mean values of Lymphocytes were significantly lower in severe category patients, whereas values for Neutrophils, D-dimer, CRP and Ferritin were significantly higher in patients with severe disease than those in moderate and mild category. [25-26]

5. On comparing the co-morbidities with clinical severity of Covid 19 in our study, results showed that there is no significant association between diseases like Asthma, COPD and epilepsy with clinical severity of covid 19, this is probably because of smaller sample size of such patients. Whereas IHD, DM and HTN shows significant correlation between presence of such co-morbid conditions with severity of disease (as suggested by p values <0.05). Presence of these co-morbidities associated with more chances of moderate to severe disease. [26-27]

6. On comparing the mean NLR values with Clinical severity of Covid-19 it is found that patients with severe category (5.5426) had significantly higher NLR than the moderate (3.7607) and mild category (3.0391) patients. The comparison was significant with p value of <0.001. On comparing treatment outcome with mean NLR values a significant difference was reported. Patients who expired has significantly higher NLR than those who improved in present study (p<0.001). [28-29]

7. On comparing the mean values of lab results of COVID -19 patients with outcome a significant difference was observed. Mean levels of Neutrophils, CRP, D-dimer and Ferritin was found to be increased in patients who expired as compared to those patients who improved. Whereas mean levels of lymphocytes are significantly lower in expired patients as compared to improved. [30]

8. Pearson correlation between the NLR and the inflammatory markers shows that NLR is positively correlated with D-dimer, CRP and ferritin levels. Increasing values of inflammatory markers is associated with increasing NLR values. [31]

9. On ROC analysis, area under the curve was highest for NLR (0.912) as compared to other test variables. This signifies that NLR is a significant tool in predicting the outcome in patients with Covid-19 (p<0.001). [32]

Conclusion

According to our study we can conclude that NLR ratio is a highly sensitive indicator to predict the clinical severity of disease on presentation. It can also help us to early identify severe cases so that appropriate treatment interventions can be planned and done. NLR ratio also helps us to predict risk of mortality of patients and their end outcomes. NLR correlates with other inflammatory markers like Serum Ferritin, D-dimer, and CRP to give us an idea about overall inflammatory status of the patient. Our study also helps us to identify increasing age as an independent risk factor for more severe disease. Also, that clinical characteristics like Pulse rate, respiratory rate, and Oxygen saturation on presentation can be individually used to predict disease severity and outcome. Various comorbid conditions like DM, IHD and HTN are significantly related to more moderate to severe disease severity. By using NLR values, other inflammatory markers, and correlating it with clinical parameters at presentation, we can early identify patients who are going to develop serious disease and need more intensive care and management. It can further help in developing guidelines for monitoring of covid 19 patients.

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